Epidemiological Aspects of Penile Cancer in Minas Gerais: Evaluation of 55 Cases from Two Referring Hospitals

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ABSTRACT

BACKGROUND: Penile cancer is an uncommon neoplasm, usually found in populations with low income and education. Although about 80% of all cases can be cured, the treatment for this disease has devastating consequences for the patients, and public task has to be taken in order to minimize this health problem. The aim of this study was to analyze the epidemiology of penile cancer from two referring hospitals in Minas Gerais state (Brazil).

METHODS: From October 2012 to November 2014, 55 patients with penile cancer were evaluated according to age, socioeconomic factors, risk factors and TNM staging. Surgical specimens were reviewed and all tumors histologically classifiedby two experienced pathologists.

RESULTS: The epidemiological profile of penile cancer patients in Minas Gerais state shows that they were on average married, with low education, over 40 years old and mostly did not show any family history. Most patients were smokers, 30% of them presented phimosis and 41.8% were HPV+ patients.

CONCLUSIONS: The results of this study offer a good explanation to the reason why penile cancer correlates strongly with precarious socioeconomic conditions. They also suggest that most penile cancer risk factors are preventable ones, and that such neoplasm may have its incidence drastically lowered if the proper educational measures are taken.

INFORMAÇÕES

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INTRODUCTION

Penile cancer (PC) is an uncommon neoplasm, usually found in populations with low income and education, most often in developing countries or regions, regardless of ethnic origin[1,2]. The highest incidence, as much as 1% of all men before the age of 75, is seen in Uganda[3] and the lowest, up to 300-times less, is found among Israeli Jews[4]. In Brazil, it can represent nearly 17% in prevalenceof all malignant neoplasms in men in some areas[5]. On the other hand, in places such as Europe and the United States, this number does not exceed 1%6.

Regarding age, penile cancer is usually found in men older than fifty (with a peak incidence at age of 60), though a significant 26% of patients are younger than forty[3]. Penile cancer is usually found in the glans (48%), prepuce (21%) or both (9%). Other usual sites are the coronal sulcus (6%) and the shaft (less than 2%)[7]. Although many variants are known, about 95% of penile cancer cases come in the shape of in situ and invasive squamous cell carcinomas[1, 5, 8, 9].

A well-known risk factor for this disease is phimosis, which can be found in 25-60% of patients[1-3,5]. This increase on cancer likelihood, which may be as much as 3.5-fold, is likely related to the difficulties in maintaining hygiene caused by the foreskin, which may lead to chronic inflammation when associated with Mycobacterium smegmati[10]. Neonatal circumcision is known to be a preventive factor, drastically reducing the number of cases[7], 11, 12. Beyond that, other factors that

may affect penile cancer incidence are infection by Human Papiloma Virus (HPV) (which is found in between 30 and 70% of penile cancer cases)[13], especially viral oncogenic types 16 and 18 (14-16), tabagism and multiple sexual partners (that may be related to a higher virus exposure risk)[17].

Regarding lymph node metastatic spread, an independent risk factor for survival in penile cancer[7] about 58% of patients will present palpable inguinal nodes, of whom 17–45% will have neoplastic cells. Because secondary inflammation due to infections and overall tumoral irritation is also a cause of positive lymph nodes, clinical diagnosis of nodal involvement is inaccurate, requiring other resources such as biopsy for a better diagnosis[18].Recent published paper has shown 18F-FDG PET/CT a promising diagnostic tool to evaluate lymph node involvement[19]. However, more data is needed to confirm its routine clinical use.

Although about 80% of all cases can be cured5, the treatment for this disease has devastating consequences for the patients, both physically and mentally, and public task has to be taken in order to minimize this health problem. Thus, the aim of this study was to analyze the epidemiology of penile cancer from two referring hospitals in Minas Geraisstate (Brazil).

MATERIAL AND METHODS

From October 2012 to November 2014, 55 patients with histologically confirmed penile cancer referred to 2 local hospitals in Minas Gerais were evaluated prospectively. The study was approved by the local ethical committee. All patients gave their informed consent to participate in the study.

Patients were assessed according to the following epidemiological data: age, socioeconomic factors (such as marital status and education level), risk factors (such as family history, smoking, phimosis and previous surgery, lymph node metastasis) and TNM staging.

The clinical and pathological staging was done according to the 2009 TNM classification. Two experienced pathologists, unaware of the clinical results, performed the histopathological analysis. TNM classification (AJCC Cancer Staging Manual, 7th ed.) and the current WHO (World Health Organization Urological Malignancies Staging System)[20] criteria for tumor grading were adopted. The pathological variables studied were: histological type, grade, size of the lesion, tissue infiltration and lymphovascular infiltration. Beyond that, we also sought evidences of HPV infection, in the shape of koilocitosis.

Data were analyzed descriptively and expressed as absolute and/or relative value, mean ±standard deviation, when available, with agreement rations (kappa) calculated by Medcalc version[12.4].

RESULTS

Between the onset of symptoms and the diagnosis of penile cancer, there was an average of 14.4 ± 16.4 months (range 0-96 months). The 55 patient's ages ranged from 26 to 84 years, with a mean of 56.6 ± 13.6 years. Of the total evaluated, only 7 (12.7%) were 40 years or less.

The education level ranged from illiterate (10.9%) to high school graduates (7.3%), with a majority of patients (76.3%) presenting low education level. More than half of the patients were, at some point, married (58.2%), whilethe marital status of 4 patients (7.3%) was unknown (Table 1).

TABLE 1 - Educational and Marital Status Level of Penile Cancer Patients

Variables	Absolut		Accumulated	
	Frequency	%	Frequency	%
Educational Level				
Illiterate	6	10.9	6	10.9
Incomplete Elementary School	26	47.3	32	58.2
Elementary School Graduates	10	18.1	42	76.3
High School Graduates	4	7.3	46	83.6
Unknown	9	16.4	55	100.0
Total	**55**	**100.0**	-	-
Marital Status				
Married	27	49.1	27	49.1
Divorced	3	5.5	30	54.6
Single	19	34.5	49	89.1
Widowed	2	3.6	51	92.7
Unknown	4	7.3	55	100.0
Total	**55**	**100.0**	-	-

Regarding risk factors, only one patient (1.8%) had family history of the disease, thirty-two patients (58.2%) were smokers and seventeen patients (30.9%) had phimosis.In relation totumor site, the glans was, by far, the most common

area affected in 43 (78.2%) patients. Among them, the glans was the exclusive place of tumor growth in 25 (45.5%) patients, while the glans and the shaft were affected together in 16 (29.1%) men analyzed. The glans and the foreskin were affected in 2 (3.6%) patients. Three patients (5.5%) were affected solely on the foreskin. Other tumor sites were seen in 9 (16.3%) patients.

The clinical TNM stagingrevealed cT2 (43.6%) the most common tumor stage, followed by cT1 (32.7%), cT3 (20.0%) and cT4 (3.7%). Regarding the regional lymph nodes, 54.5% of the patients presented as cN0, 32.7% as cN2, 7.3% as cN1 and 5.5% as cN3 (Table 2).

TABLE 2 - Clinical staging of penile cancer patients

Staging	Absolut		Accumulated	
	Frequency	%	Frequency	%
T (tumor)				
1	18	32.7	18	32.7
2	24	43.6	42	76.3
3	11	20.0	53	96.3
4	2	3.7	55	100.0
Total	**55**	**100.0**	-	-
N (node)				
0	30	54.5	30	54.5
1	4	7.3	34	61.8
2	18	32.7	52	94.5
3	3	5.5	55	100.0
Total	**55**	**100.0**	-	-

All patients underwent surgical treatment, as follow: biopsy or local resection (n=6, 10.9%), partial penectomy (n=40, 72.7%) and total penectomy (n=9, 16.4%), which could be accompanied by unilateral (n=3,5.5%) or bilateral (n=27, 49.1%) lymphadenectomy. The treatment choice for each patient was defined based on European Guidelines for penile cancer[8].

Regarding the histopathological TNM analysis, 2 patients (3.6%) were staged as In situ carcinoma, 7 (12.7%) were staged as pT1a, 2 (3.6%) as pT1b, 29 (52.7%) as pT2 and 15 (27.4%) as pT3. In relation to lymph nodes, 25 (45.5%) were staged as pNx, 14 (25.5%) as pN0, 1 (1.8%) as pN1, 5 (9%) as pN2 and 10 (18.2%) as pN3 (Table 3).

TABLE 3 - Pathological staging of penile cancer patients

Staging	Absolut		Accumulated	
	Frequency	%	Frequency	%
T (tumor)				
"In situ"	2	3.6	2	3.6
1a	7	12.7	9	16.3
1b	2	3.6	11	19.9
2	29	52.7	40	72.6
3	15	27.4	55	100.0
Total	**55**	**100.0**	-	-
N (node)				
x	25	45.5	25	45.5
0	14	25.5	39	71.0
1	1	1.8	40	72.8
2	5	9.0	45	81.8
3	10	18.2	55	100.0
Total	**55**	**100.0**	-	-
M (metastasis)				
0	55	100.0	55	100.0
1	0	0	55	100.0
Total	**55**	**100.0**	-	-

DISCUSSION

Penile cancer is a rare neoplasm with low overall incidence. It is prevalent in elderly men, peaking after 40 years old, with few cases appearing earlier in life. In our study, we observed only one case (1.85%)among patients aged between 20-29 years, and 5 cases (9.09%) in men aged between 30 and 39 years. The peak incidence was found in the fifth and sixth decades of life (24% of the patients aged between 40-49 and 24% between 50-59 years).

It is important to highlight the great amount of patients for such a rare disease in a period of only 2 years. A study performed by Koifman et al[5], for instance, presented a higher patient count, but lasted a much longer period of time.

Most patients in this study had low levels of education, ranging from total illiteracy (13%) to a majority of middle school dropouts (56.5%). The highest education level found was complete high school (8.7%). This data is in accordance with previous research on the topic[5], which implies a strong correlation between low scholarity and penile cancer. We

hypothesize this is a demonstration of how penile cancer often manifests in risk populations, perhaps due to low instruction regarding proper penile hygiene.

On that aspect, this opens a window of action in the shape of public health education measures. Penile diseases are often seen as taboo and carry a heavy stigmatization, which reduces male visits to the urologist and delays diagnosis, considerably worsening the prognosis of the disease. Due to that, the finding and identification of the neoplasm are often done at advanced stages. This can be added to the fact that penile cancer, being a rare disease, is highly neglected both by the populations and by the public healthcare system itself.

Regarding marital status, out of the fifty-five patients evaluated, 32 (62.7%) were at some point married. This is controversial, since literature points out that married men have lower penile cancer incidence, when compared to single ones[17, 21]. It is important to emphasize, however, that penile cancer incidence is related to sexual habits and promiscuity rather than marital status in itself. Moreover, cultural habits regarding lack of condom usage play a large effect on HPV incidence and as such, on penile cancer cases. Zoophilic practices, which can sometimes be observed in populations with low scholarity and socioeconomical level, may also have a role to play in the rates of penile cancer.

Koilocytes, a particular cell alteration which has undergone mutations caused by HPV infection, were found in 41.8% of patients. The infection was highlighted by the sample's alterations in eosinophilia, also found in 41.8% of subjects. HPV, especially subtypes 16 and 18, is known to cause expression of proto-oncogenes, which in turn cause unrestrained cellular division, DNA mutation and cell immortalization, followed by tumor genesis[14-16]. The virus integrates its DNA into the host, which leads to overexpression of viral oncoproteins E6 and E7. E7 inhibits tumor suppressor proteins RB, p21 and p27, and activates cyclins E and A. E6 degrades p53 and BAX inhibiting apoptosis, and activates telomerase fighting cell senescence.

Bearing in mind recent changes to Brazilian vaccinecalendar, which included the addition of a four-serotype HPV vaccine in females at the age of nine, we suggest further studies and investigations regarding the prevalence of this virus in the general populace and how it can impact penile cancer epidemiology.

The glans was the point of maximum tumor invasion and the shaft and preputial ring were also affected. This reinforces the importance of HPV in the development of penile cancer, as these anatomical regions are also the first areas affected by condyloma acuminata, a benign disease caused by HPV 6 and 11.

Concerning congenital risk factors, only one (1.8%) patient had any family history on penile cancer. Therefore, we infer there is little to no heredity regarding this neoplasm, making genetics a low relevance liability in this kind of tumor. These findings contradict what is usually observed in most types of cancer.

This scenario may bring a difficulty in penile cancer control, since the lack of familial history increases the likelihood of neglect in screening of this neoplasm, as opposed to cases such as breast or prostate cancer. On the other hand, penile cancer is a disease with can easily be prevented merely by spreading information about the importance of proper penile hygiene habits.

The average time between symptoms onset and clinical diagnosis was 14.4 ± 16.4 months, ranging from 0 to 94 months. This delay may too be associated with the patient's low socioeconomic profiles, with the difficulties involved in gaining access to public healthcare and with the stigmatization which revolves around the disease.

A strong association between penile cancer and use of tobacco has been previously demonstrated[13]. This link could be clearly observed in our study, where out of the observed fifty-five subjects, thirty-two (58.2%) were smokers. Therefore, smoking might be presented itself as a risk factor in this study, though the mechanisms involved in such process are yet to be elucidated.

It was observed that 30% of our patients had phimosis, which is in agreement with data found in literature (it is normally expected that 25-75% of the patients will have phimosis)[3]. Those results come due to the chronic inflammation caused by the excessive foreskin, which can be worsened by the precarious hygiene habits often observed in low-income and low education populations.

When analyzing the clinical TNM staging, we found out that the most common stages were T1 (32.7%) and T2 (43.6%) for tumors. While T3 is not uncommon (20.0%), T4 incidence was low, found in just 3.7% of the patients. For node involvement, however, the most common stages were N0 (54.6%) and N2 (32.7%), being N1 and N3 quite rare (7.3 and 5.5% respectively).

This data shows a disagreement between the clinical and histopathological staging of T (kappa 0.122; CI95%0.0611 to

0.306). The staging of lymph nodes also had a low agreement ratio(kappa 0.396; CI95% 0.209 to 0.583), with N0 being the most common in clinical staging (54.5%), whereas most lymph nodes analyzed histopathologically were found to be indeterminate (45.5% of nodes were staged as Nx).

This high disagreement may be due to difficulties intrinsic to the clinical exam: definition of T relies on visual information which does not always correlate to a tumor's real size and infiltration. Beyond that, a clinically positive lymph node is defined exclusively by being palpable; an enlarged lymph node, however, may be caused by inflammation secondary to the base disease, which does not necessarily implicate in the presence of metastatic cells in the node.

CONCLUSION

The epidemiological profile of penile cancer patients in Minas Gerais state shows that they were on average married, with low education, over 40 years old, mostly did not show any family history, most patients were smokers, some of them presented phimosis and had signs of HPV+.

These results offer a good explanation to the low prevalence of penile cancer in developed countries and why it correlates strongly with precarious socioeconomic conditions. The data above suggests that most penile cancer risk factors are preventable ones, and that such neoplasm may have its incidence drastically lowered if the proper educational measures are taken, spreading information about proper penile hygiene, HPV prevention and tobacco use.

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